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## REMARKS

Background

This application has been carefully reviewed in light of the Office Action mailed March 15, 1990. Claims 40-52 stand withdrawn from further consideration as being drawn to a non-elected invention. Claims 1-39, 52, 55, 61-65, 75 and 77 have been cancelled. Claims 54, 56-60, 66-74, 76 and 78-82 are presently under consideration. Claim 72 has been amended above. Support for this amendment is found in the priority application, then-pending claim 25 (twice amended) and in the specification. This amendment and remarks are submitted in response to the Office Action. In light of this amendment and the personal interviews between the Examiner and Applicant's attorney, Applicant believes that the claims are now in condition for allowance and respectfully requests that the application be reexamined.

In reviewing the present Office Action, Applicant has noticed that this Office Action, dated March 15, 1990, is actually an identical copy of an Office Action issued in the previous prosecution of the above-identified application (except that the application Serial No. referred to in the first full paragraph on page 5 has been changed). This previous Office Action corresponds to the first Office Action issued in connection with a File Wrapper Continuation application dating back to January 9, 1987, Serial No. 002,014. Since the June 11, 1987 Office Action, two File Wrapper Continuation applications have been filed, including the above-identified application. These File Wrapper Continuation applications have resulted in significant progress in prosecuting the present application as now claimed.

The progress referred to relates to the present rejection under 35 U.S.C. 102(e) which was initially issued in the Office Action mailed November 27, 1985, in connection with the priority application, Serial No. 314,124. This rejection was finally withdrawn in the previous Office Action, dated March 22, 1989,

issued in connection with the parent case, Serial No. 140,916. In the second paragraph on page 2 of the March 22, 1990, Office Action, the Examiner states:

> "The rejection under 35 U.S.C. 102(e) or in the alternative under 35 U.S.C. 103 over T'so et al. ('863) (Office Action mailed November 14, 1988, paragraph running from pages 3 through 5) is withdrawn in view of the Declaration under 37 C.F.R. 1.131 filed March 7, 1989. It has been presumed that the exhibits referred to in the declaration by Roman numerals are actually the exhibits accompanying the declaration that are labeled with Arabic numerals."

As a matter of clarification, Applicant confirms that the exhibits to the Declaration previously submitted were incorrectly labeled with Arabic numerals rather than Roman numerals, as indicated in the Declaration. Any resulting inconvenience is regretted.

In light of the above, Applicants assume that the rejection in the present Office Action under 35 U.S.C. 102(e) or 103 was mistakenly overlooked by the Examiner and simply not removed from the text of the present Office Action since this rejection was removed in the Office Action of March 22, 1989. Therefore, the rejection of the claims as anticipated by or, obvious over T'so et al. is, as it was, removed.

The Amendment

The specification is objected to and claim 72 stands rejected under 35 U.S.C. 112, first paragraph. The Examiner states that the sequence recited in claim 72 is the reverse of the sequence recited on page 19 of the specification. The Examiners attention is drawn to Applicant's Amendment to the priority application mailed

February 7, 1984. On page 13 of that paper, Applicant in response to a similar rejection, pointed out that the base sequence of the then-pending claim 25 (which corresponds to the pres ntly-pending claim 72) corresponds to a 3' to 5' reading of the s quence giv n on page 19 of the application, the latter being presented as a 5' to 3' sequence. Because of formalities, the claim was finally amended correctly to clearly indicate the direction of reading in Applicant's amendment dated December 4, 1984. Subsequently, the then-pending claim 25 was not rejected again for the reason set forth above until three Office Actions later.

In the last Office Action of the priority application, dated July 15, 1986, the now-pending claim 72 was again rejected under 35 U.S.C. 112, first paragraph and has continued to be rejected for being the reverse of the sequence recited on page 19 of the specification. At that point in time, the sequence in claim 72 was identical to one of the four sequences listed on page 19 depending on whether $R_1$ and $R_2$ was G or T. The origin of these sequences are explained in the first two full paragraphs on page 19 and depicted diagrammatically in Figure 7 of the application. In regard to this rejection, Applicant mistakenly amended the claim to read in the wrong direction (i.e., from 3' to 5'). Claim 72 has been amended above to clearly indicate that the sequence is reading from 5' to 3'. This sequence as now amended <u>absolutely</u> corresponds to the non-coding strand for follicle stimulating hormone (FSH) and therefore is complementary to FSH mRNA. It will hybridize to codons 33 through 40 as supported by the specification on page 19 and in Figure 7. The rejection of claim 72 under 35 U.S.C. 112, first paragraph should therefore be removed.

<u>The Prosecution History</u>

In the present Office Action, the Examiner has continued to maintain the rejections under 35 U.S.C. 103 from the previous March 22, 1989 Office Action as being unpatentable over Itakura et al. in view of Peterson et al. or Hastie et al. and furth r in view of

Summerton or Miller et al. (Bioch m. 16:1988). The Examiner states that Miller et al. teaches the inhibition of cellular protein synthesis due to the binding of oligoribonucleotides to cellular mRNA and also suggests the use of longer oligonucleotides to increase the specificity of inhibition. He additionally alleges that oligonucleotide synthesis has long been routine in this art and cites Miyoshi as of interest. The Examiner alleges further that Applicant's arguments are not persuasive because Summerton discloses oligodeoxynucleotides to be taken up by cells.

The prosecution history of the application will be briefly reviewed as it is believed to bear directly on the grounds of rejection now at issue. The priority case was filed October 23, 1981. The original set of claims 1 to 52 (and claim 53 added by amendment) were examined in a series of Office Actions culminating in an Action made final on August 8, 1985. At that point there were two general grounds of rejection.

1) The claims were alleged to be non-enabled under 35 U.S.C. 112.

2) Claim 1 and its dependents relating to synthesizing a therapeutic oligonucleotide were rejected under 35 U.S.C. 103 over Itakura et al. in view of Paterson et al. or Hastie et al. Claim 1 and its dependents relating to synthesizing a therapeutic oligonucleotide were rejected over Itakura et al in view of Paterson et al. or Hastie et al. Claim 1 and its dependents as well as claims to a method of controlling activity of specific biological components in a cell (claim 20 and its dependents), to a method of inhibiting infection in a host organism (claim 31 and its dependents) and to a method of therapy (claim 53) were rejected over the above-references, further in view of any one of Pluskal et al., Pitha, Befort, Arya et al., Summerton, Tennant, Miller, Stephenson et al., Zamecnik et al. and Stebbing et al.

In response, Applicant, his attorn ys and a representative of the assign e m t with the Examiner on October 18, 1985. At that time, the outstanding rejections of th claims were discussed at length and a revis d set of claims, refl cting th Examiner's suggestions, were presented. The Examiner's Interview Summary Record is considered particularly important and is reproduced in part, below:

> "In view of intent to limit claims to oligodeoxyribonucleotides, the 112 rejections bridging pages 2 through 3 and last full paragraph on page 3 will be withdrawn. Applicant intends to avoid 112 rejection bridging pages 3 through 4 by amendment. Applicant argued that instant invention differs from Miller et al. (1981) in that Miller uses shorter oligonucleotides that bind to tRNAs leading to non-specific effects while instant application deals with specific inhibition by binding to coding region of mRNAs (e.g. T Ag mRNA = 0.01% total message). Examiner pointed out that claims not limited to oligonucleotide size. Examiner favorably impressed with argument in connection with reference dealing with 5' repeat sequences in RNA (e.g., Zamecnik). Pending limitation of claims Examiner favorably impressed regarding argument in connection with all 103 rejections. In view of new Miller et al. (United States Patent No. 4,511,713) reference Examiner will make supplementary office action obviating the need of applicant to respond to the action May 8, 1985. . . ."

At the interview, the Examiner indicated that he would be issuing a suppl mentary Office Action, in light of a recently issued pat nt to b cited under 35 U.S.C. 102(e). In addition to rejecting all claims over T'so under 35 U.S.C. 102(e), this Office Action, dated Novemb r 27, 1985, repeat d th earlier rejections under 35 U.S.C. 112 and 35 U.S.C. 103. In a telephone conversation between Examiner and the undersigned attorney, the Examiner indicated that these earlier rejections were repeated merely for formal reasons. (This conversation is referred to in Applicant's paper 19, page 10).

Applicant thereafter amended all claims, in accordance with those proposed by Applicant and reviewed by the Examiner in the interview. A further series of Office Actions and responses, which necessitated the filing of continuation applications, culminated in the rejections over reference to T'so being withdrawn in an advisory action dated March 22, 1989. However, rejections over references cited prior to the interview of October 18, 1985, continued to be maintained, despite the fact that it was believed that the references had been distinguished by amendments to the claims in accordance with the discussion at the interview on October 18, 1985.

In a further interview between the undersigned attorney and the Examiner on August 23, 1989, these remaining grounds of rejection were once again discussed at some length. The attention and courtesy of the Examiner at that time are greatly appreciated. As indicated in the Examiner Interview Summary Record, the Examiner indicated that the lack of specificity of protein inhibition which could be achieved using merely a triplet, as disclosed in Miller et al., was a strong argument against the obviousness of the highly specific inhibition of protein synthesis obtained by the claimed use of oligonucleotides. Moreover, the age of the cited references, which range between 1977 and 1980, indicate that Applicant's invention was not, in fact, obvious at the time.

Moreover, Applicant's attorney pointed out that th synth sis and subsequ nt isolation of phosphotriesters was neith r obvious nor trivial at the time of the invention. Further, th distinctions of the present invention, which uses oligodeoxyribonucleotides specifically to inhibit protein synthesis in vivo and the prior art methods of Hastie and Miller were discussed. As to the Examiner's response the Examiner Interview Summary Record indicates that the Examiner was "favorably impressed."

The Present Rejection

The claims now stand rejected under 35 U.S.C. 103, for reasons stated in the Office Action of November 14, 1988, first full paragraph on page 3, which in turn refers to the Office Action of November 27, 1985. As outlined above, the Examiner previously indicated these rejections were restated merely for formal reasons in this Office Action subsequent to the first interview. The cited references are Itakura, in view of either Paterson et al. or Hastie et al. and further in view of either Summerton or Miller. Thus the status of the application is as it was at the time of the personal interview on October 18, 1985, at which time it was believed that the claims were distinguishable over the then, as now, cited art.

Itakura et al. discloses the synthesis of oligonucleotides while Hastie et al. and Paterson et al. disclose hybrid arrested translation (HART) using full length cDNAs (i.e., polynucleotides). For reasons already made of record in the December 4, 1984 Amendment (page 7 through paragraph bridging pages 10 and 11) and believed by Applicants to have been accepted by the Examiner during subsequent interviews, the claimed invention has already been distinguished and shown to be non-obvious over these cited references.

In the Amendment dated December 4, 1984, pertinent distinctions were made between the methods disclosed in the present application and those of the cited art. The first distinction

relates to the size of th nucleic acid segments used to inhibit protein synthesis. Both cited ref rences teach the use of large polynucleotides to accomplish translation arrest whereas the present application teaches the use of small oligonucleotides. The second distinction, although related to size, concerns the kinetics of hybridization of polynucleotides compared to oligonucleotides. Oligonucleotides will spontaneously hybridize at body temperature whereas polynucleotides will not. These distinctions will again be expanded on below.

In regard to the size of the nucleic acid segment used to accomplish translation arrest, at the time the invention was made, those skilled in the art believed that such short oligonucleotides would not efficiently inhibit translation arrest; hence, the reason that the cited prior art disclosing hybrid arrested translation employs only full length cDNAs and not oligonucleotides to achieve efficient inhibition.

The reason for the above belief relates to the binding energy of a hybridized nucleic acid. The more base pairs (bp) which are hybridized in a duplex, the more hydrogen bonds are formed, and therefore, the more stable a particular duplex will be. Thinking at the time the application was filed was that an oligonucleotide in duplex formation with a mRNA would not be stable enough to prevent ribosomes from translocating down the message because of the small number of base pairs formed. Thus, the ribosomes would essentially knock a hybridized oligonucleotide off a message during translation. Therefore, the demonstration that oligonucleotides inhibit mRNA translation as disclosed in the present application is in fact an unexpected result and cannot be considered obvious over the cited art. As discussed in the December 4, 1984 Amendment, this conclusion is corroborated by the fact that, including the Miller et al. and Zamecnik and Stephenson references, no other <u>analogous</u> experiments using short oligonucleotides were known at the time. (Miller et al. discloses the non-specific

inhibition of protein synthesis while Zamecnik and Stephenson are distinguished because the claimed invention hybridizes to the coding region which is rich in secondary structure.)

In regard to the spontaneous hybridization of oligonucleotides at body temperature, there are two factors which render the use of oligonucleotides non-obvious over the above-cited art. The first involves the melting temperature ($T_m$) of a duplex (either hetero or homoduplex). Irrespective of the fact that once hybridized a duplex is more stable at a lower temperature, the optimal temperature for hybridization (i.e., renaturation or annealing) is approximately 25°C below the $T_m$. The reason for this phenomenon is that the rate limiting step in reassociation of two complementary nucleic acids is the initial pairing of a few base pairs within the sequences (i.e., a second order nucleation step). If the hybridization temperature is too high, the two molecules will not find each other due to kinetic energy. Conversely, if the hybridization temperature is too low, renaturation will also not occur between complementary molecules because each strand will form internal secondary structures with itself. This is a more preferred unimolecular reaction (i.e., first order "quenching" step) when the temperature is too low then a bimolecular renaturation reaction. At the time the invention was made, those DNAs known to efficiently inhibit translation were long polynucleotides (on the order of 1000 bp). The use of polynucleotides of this length in vivo (i.e., 37°C) would be renaturing the complementary strands at too low of a temperature. The molecules would form internal secondary structures and not hybridize with their complements to inhibit translation. Oligonucleotides as disclosed in the present application, on the other hand, have optimal $T_m$ for complete hybridization at body temperature.

The second factor regarding the spontaneous hybridization of oligonucleotides is th actual kinetics of renaturation ind pendent

of $T_m$. Oligonucleotides will renature faster than larger polynucleotid s. This phenomenon reflects th complexity of the sequences involved and is proportional to the number of base pairs but also relates to the uniqueness of the sequence. The small compl xity of oligonucleotides allows a mor rapid and complet hybridization to efficiently inhibit translation.

The cited references of Itakura et al., Hastie et al. and Paterson et al., alone or in combination, do not teach or suggest the use of oligonucleotides complementary to the coding region of mRNA to inhibit the synthesis of specific proteins in vivo. The tertiary references of Summerton and Miller et al. also do not render the claimed invention obvious. Summerton teaches the use of polynucleotides having crosslinking agents attached to them. The polynucleotides are complementary to the totality of infective viral DNA. When the polynucleotides contact viral DNA, the crosslinking moieties crosslink the two sequences, inactivating the viral DNA. Of critical importance, Summerton does not suggest that DNA devoid of crosslinking moieties could inhibit protein synthesis or inactivate specific DNA sequences. In fact, his approach requires crosslinking moieties, thereby suggesting that noncrosslinkable polynucleotides, especially oligonucleotides, could not serve to inhibit protein synthesis. The fact that Summerton discloses oligodeoxynucleotides to be taken up by cells is irrelevant.

Directing the Examiner's attention to the tertiary reference of Miller et al., as stated above, the Examiner alleges that Miller et al. teaches the inhibition of cellular protein synthesis by the binding of oligoribonucleotides to cellular mRNA and also suggests the use of longer oligonucleotides to increase the specificity of inhibition. As of interest, Miyoshi is cited to support the contention that oligonucleotide synthesis has long been routine.

Mill r et al. discloses experiments relating to the use of the phosphotriester ribonucleotide trimer GGU to inhibit cellular prot in synthesis in fibroblasts. Inhibition of prot in synthesis using only a trimer differs in both m chanism and in the specificity achieved from the method of the present invention. The GGU trimer of Miller et al. is complementary to three translational components: (1) the amino acid accepting stem of most tRNAs, (2) the anti-codon of the $tRNA^{gly}$ and (3) the codon corresponding to the amino acid threonine. The experimental evidence presented in the Miller reference suggests and focuses only on binding to the first component above (i.e., the accepting stem of tRNAs). Additionally, while it is correct as the Examiner has stated, that the Abstract refers to binding of the trimer to mRNA, in fact, there is no support for such binding in the data. Rather, using a complementary trimer to tRNA stem sequences, Miller teaches the global inhibition of protein synthesis by preventing aminoacylation of tRNAs. The claimed invention, on the other hand, uses oligonucleotides complementary to mRNA coding regions to prevent protein synthesis by inhibiting ribosome translocation, not merely aminoacylation of tRNAs. Moreover, this mechanism of inhibition in the claimed invention is sequence specific and inhibits th synthesis of specific proteins.

As for Miller's referral of the trimer binding to mRNA, there is no question as to whether a trinucleotide of any sequence will bind to any mRNA. Because of the shortness in sequence, a trimer will bind to any mRNA with a probability of once in every sixty base pairs. Specifically, the trinucleotide used by Miller, GGU, will bind to every threonine codon. Since most proteins contain this amino acid, specific inhibition of a targeted protein is impossible using only a trimer.

As the Examiner has pointed out, the Miller reference remarks in the last paragraph that oligoribonucleotides "having longer chain lengths and greater resistance to hydrolysis" would

provide greater specificity and effectiven ss in inhibiting targeted nucleic acids. This statement can only be considered wishful thinking. C rtainly it do s not provide an enabling disclosure such that one skilled in the art would, even in light of the additional prior art cited, be able to accomplish Applicant's invention without undue experimentation. If it were obvious, and if Miller could have synthesized longer oligoribonucleotides then, why had he not done it? As previously stated, it is also not obvious that oligodeoxyribonucleotides would necessarily have the same effect. As the courts have recently made explicitly clear, the mere fact that a solution to a problem is obvious to try does not render a final product obvious. American Hospital Supply Corp. v. Travenol Laboratories, Inc. 727 F.2d 1524, 1530 (Fed. Cir. 1984) (" 'obvious to try' is not a legitimate test of patentability under Section 103.") Given the state of the art at the time of the invention and Miller's inability to produce longer phosphotriester oligonucleotides, one would have been led to conclude that the Applicant's invention would be neither practical nor effective.

Moreover, the Examiner's citation of Miyoshi as alleging routine synthesis of oligonucleotides is indicative of th inability to successfully produce longer phosphotriesters. Miyoshi synthesized a homopolymer (i.e., a nineteen nucleotide oligomer with just thymidine). Given the history of polymer synthesis, this reference suggests that either synthesis or purification of oligonucleotides with other nucleotide bases was inefficient or unsuccessful at the time. In fact, Miyoshi himself alludes to these problems by stating "solid phase synthesis of oligonucleotides has not been as successful as that of protein synthesis" and "extension of the [phosphotriester] methodology to the synthesis of oligonucleotides containing all four bases is currently under investigation" (first and last sentences of the paper respectively).

Even if the synthesis of oligonucleotides was routine at the tim the invention was made, the methods disclosed by Miyoshi are non-analogous to those disclosed in the present application. Miyoshi does not produc , nor can he produce, oligonucleotide triesters as products. Instead, Miyoshi uses phosphotriester synthesis methods to produce normal, unmodified oligonucleotide diesters. Thus, the cited references of Miller et al. and Miyoshi et al., either alone or in combination, do not teach nor suggest the methods disclosed in the present application. Applicant maintains, in light of all the above arguments, that the rejection under 35 U.S.C. 103 should be removed.

In light of the amendment and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call Applicant's attorney, Cathryn Campbell, at (619) 535-9001, facsimile (619) 535-8949.

Respectfully submitted,

Cathryn Campbell
Registration No. 31,815

PRETTY, SCHROEDER,
BRUEGGEMANN & CLARK
444 South Flower Street, Suite 2000
Los Angeles, California 90071

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By
Cathryn Campbell Reg. 31,815
July 6, 1990
Date of Signature